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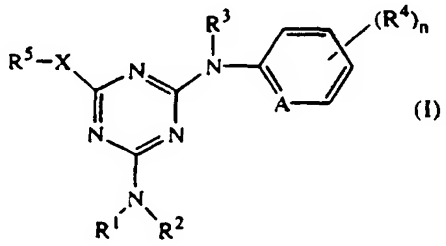
(54) Trisubstituted 1,3,5-triazine derivatives for treatment of HIV infections

(57) This invention concerns the use of the compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein A is CH or N; n is 0, 1, 2, 3 or 4; and in case A is CH, then n may also be 5; R^1 and R^2 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally be substituted; or R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene; R^3 is hydrogen, aryl, C_{1-6}alkylcarbonyl, optionally substituted C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl; and each R^4 independently is hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ; R^5 is optionally substituted phenyl; and X is -NR^3-, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -$S(=O)_2$-; aryl is optionally substituted phenyl; Het is an optionally substituted aliphatic or optionally substituted aromatic heterocyclic radical; for the manufacture of a medicine for the treatment of subjects suffering from HIV (Human Immunodeficiency Virus) infection. It further relates to new compounds being a subgroup of the compounds of formula (I), their preparation and compositions comprising them.

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Description

[0001] The present invention is concerned with trisubstituted 1,3,5-triazine derivatives having HIV replication inhibiting properties. The invention further relates to methods for their preparation and pharmaceutical compositions comprising them. The invention also relates to the use of said compounds in the manufacture of a medicant useful for the treatment of subjects suffering from HIV (Human Immunodeficiency Virus) infection.

[0002] Compounds structurally related to the present compounds are disclosed in the prior art.

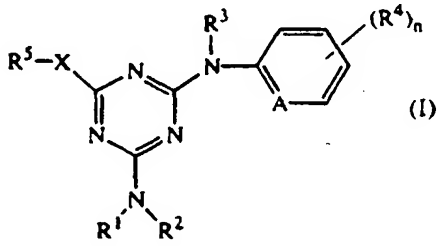
[0003] Zerkowski et al. in Chem. Mater. (1994), 6(8), 1250-1257 discloses 4-[[4-amino-6-[(4-iodophenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile and is used in the study of the crystal structure of H-bonded complexes.

[0004] US-2,671,810 discloses 4-cyano-anilino substituted 1,3,5-triazines useful as plasticizers, surface-active agents and as parfume ingredients.

[0005] Brit. 701,789 discloses a process for preparing 4-cyano-anilino substituted 1,3,5-triazines.

[0006] Unexpectedly, it has now been found that the compounds of formula (1) effectively inhibit the replication of the Human Immunodeficiency Virus (HIV) and consequently may be useful for the treatment of individuals infected by HIV.

[0007] The present invention concerns the use of the compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

A is CH or N;

n is 0, 1, 2, 3 or 4; and in case A is CH, then n may also be 5;

R^1 and R^2 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C_{1-6}alkyl)amino, aryl and Het; or

R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;

R^3 is hydrogen, aryl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxycarbonyl; and

each R^4 independently is hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy ;

R^5 is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, cyano, nitro and trifluoromethyl; and

X is $-NR^3-$, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or $-S(=O)_2-$;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro and trifluoromethyl;

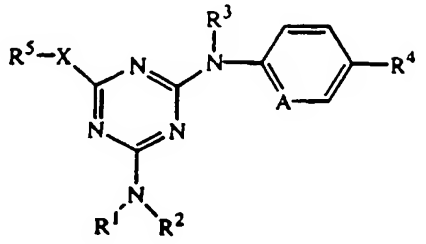
Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;

for the manufacture of a medicine for the treatment of subjects suffering from HIV (Human Immunodeficiency Virus) infection.

[0008] The present invention also relates to a method of treating warm-blooded animals suffering from HIV (Human Immunodeficiency Virus) infection. Said method comprises the administration of a therapeutically effective amount of a compound of formula (I) or a *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric

form thereof in admixture with a pharmaceutical carrier.

[0009] This invention also concerns novel compounds of formula



(I')

wherein

the variables R^1, R^2, R^3, R^5, A and X are as defined in formula (I); and
R^4 is cyano, nitro or trifluoromethyl;
with the proviso that

- when R^4 is cyano, R^3 is hydrogen, X is NH, R^5 is 4-cyanophenyl or 4-iodophenyl, then NR^1R^2 is other than NH_2, $NH[CH_2CH_2N(C_2H_5)_2]$, $N(C_2H_5)_2$, $NHCH_3$, NHC_2H_5 or NH(4-cyano-phenyl);
- when R^4 is trifluoromethyl, R^3 is hydrogen, X is NH, R^5 is 4-trifluorophenyl, then NR^1R^2 is other than NH_2 or $N[(CH_2)_6CH_3]_2$;
- when R^4 is nitro, R^3 is hydrogen or methyl, X is NH or N-CH_3, R^5 is 4-fluorophenyl, 2,6-dimethylphenyl, 4-methylphenyl or 4-nitrophenyl, then NR^1R^2 is other than NHaryl, NCH_3aryl, $N(aryl)_2$, NH_2, $NH[CH_2CH_2N(C_2H_5)_2]$, $NH[CH_2CH_2N(CH_3)_2]$, $NH[CH_2C(=O)OC_2H_5]$, $NH[CH_2C(=O)OH]$ or $N(C_2H_5)_2$;
- when R^4 is nitro, R^3 is hydrogen, X is $S(O)_2$ or S, R^5 is phenyl or 4-chlorophenyl, then R^1 and R^2 are other than aryl or C_{1-12}alkyl substituted with one or more carboxyl groups;

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof.
A special group of compounds are those compounds of formula (I') wherein R^4 is cyano. Said special group is deemed novel and can be used as a medicine.

[0010] Another special group of compounds are those compounds of formula (I') wherein R^4 is cyano, and R^5 is phenyl or phenyl substituted with one, two or three substituents each independently selected from fluoro, chloro, bromo, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro and trifluoromethyl. Said special group of compounds is deemed novel and can be used as a medicine.

[0011] As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C_{1-4}alkyl encompasses the straight and branched chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl and the like; C_{1-6}alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C_{1-4}alkyl as well as the higher homologues thereof containing 5 or 6 carbon atoms such as, for example pentyl or hexyl; C_{1-10}alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C_{1-6}alkyl as well as the higher homologues thereof containing 7 to 10 carbon atoms such as, for example, heptyl, octyl, nonyl or decyl; C_{1-12}alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C_{1-10}alkyl as well as the higher homologues thereof containing 11 or 12 carbon atoms such as, for example, undecyl, dodecyl and the like; C_{1-4}alkylidene defines bivalent straight and branched chained hydrocarbons having from 1 to 4 carbon atoms such as, for example, methylene, ethylidene, propylidene, butylidene and the like.

[0012] The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) or (I') are able to form. The compounds of formula (I) or (I') which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids.

[0013] The term addition salts also comprises the hydrates and the solvent addition forms which the compounds of formula (I) or (I') are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

[0014] The term stereochemically isomeric forms of compounds of formula (I) or (I'), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) or (I') may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formula (I) or (I') both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

[0015] Some of the compounds of formula (I) or (I') may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

[0016] Whenever used hereinafter, the term "compounds of formula (I) or (I')" is meant to include also the *N*-oxides, the pharmaceutically acceptable acid addition salts and all stereoisomeric forms.

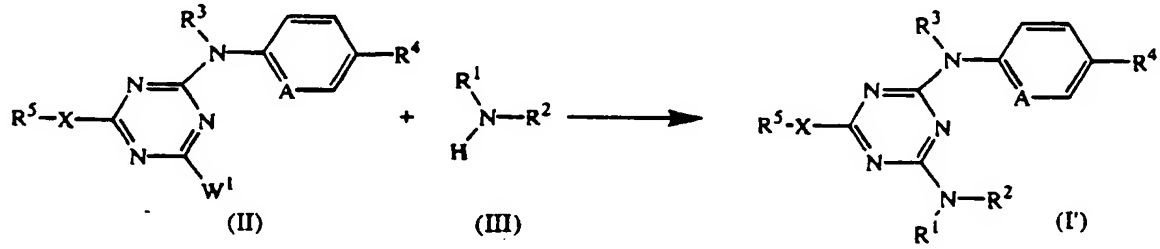
[0017] Interesting groups of compounds are those groups of compounds of formula (I) or (I') wherein one or more of the following conditions are met:

(i) n is 1;
(ii) R^1 and R^2 are each independently selected from hydrogen or hydroxy;
(iii) R^3 is hydrogen;
(iv) R^4 is cyano; and more in particular, R^4 is substituted in the 4 position relative to the NR^3 moiety;
(v) R^5 is phenyl substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl and C_{1-6}alkylcarbonyl; and more in particular the substituents are selected from fluoro, bromo, chloro, C_{1-4}alkyl and acetyl:
(vi) X is -O-, -S-, -NH- or -NH-NH-.

[0018] Preferred compounds are those compounds of formula (I) or (I') wherein R^1 is hydrogen, R^2 is hydrogen or hydroxy, R^3 is hydrogen, A is CH, n is 1, and R^4 is cyano substituted in the para position relative to the NR^3 moiety.

[0019] Also preferred are those compounds of formula (I) or (I') wherein R^5 is a 2,6-disubstituted phenyl group or a 2,4,6-trisubstituted phenyl group; in particular a 2,6-dichlorophenyl group.

[0020] In general, compounds of formula (I') can be prepared by reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group such as, for example, a halogen, with an amino derivative of formula (III) in a reaction inert solvent such as, for example, 1,4-dioxane, tetrahydrofuran, 2-propanol and the like, optionally in the presence of a suitable base such as, for example, sodiumhydroxide, sodiumhydride, triethylamine or *N,N*-diisopropylethylamine or the like.



(II) (III) (I')

[0021] In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

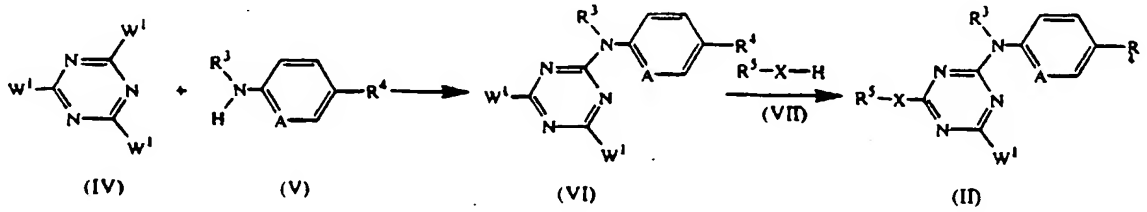
[0022] In case R^2 contains a hydroxy moiety, it may be convenient to perform the above reaction with a protected form of intermediate (III) whereby the hydroxy moiety bears a suitable protecting group P being, for instance, a trialkylsilyl group, and subsequently removing the protective group according to art-known methodologies.

[0023] The compounds of formula (I') may further be prepared by converting compounds of formula (I') into each other according to art-known group transformation reactions.

[0024] Some of the intermediates as mentioned hereinabove are commercially available or can be prepared according to art-known procedures. Of some, the preparation is described hereinbelow.

[0025] Intermediates of formula (II) can be prepared by reacting an intermediate of formula (IV) wherein W^1 is a suitable leaving group such as, for example, a halogen, with an amine derivative of formula (V) in a reaction-inert solvent

such as, for example, tetrahydrofuran, 1,4-dioxane or the like, in the presence of a suitable base such as, for example, triethylamine; and subsequently reacting the thus obtained intermediate of formula (VI) with an intermediate of formula (VII) in a reaction-inert solvent such as, for example, acetonitrile, 1,4-dioxane or the like, in the presence of a base such as, for example, potassiumcarbonate, sodium hydride, *N,N*-diisopropyl-ethylamine or the like.



(IV) (V) (VI) (II)

[0026] The order of the above reaction scheme may also be reversed, *i.e.* first an intermediate of formula (IV) may be reacted with an intermediate of formula (VII), and then, the resulting intermediate may further be reacted with an amine derivative of formula (V); thus forming an intermediate of formula (II).

[0027] Compounds of formula (I') and some of the intermediates may have one or more stereogenic centers in their structure, present in a R or a S configuration.

[0028] The compounds of formula (I') as prepared in the hereinabove described processes may be synthesized as a mixture of stereoisomeric forms, in particular in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

[0029] The compounds of formula (I) and (I') show antiretroviral properties, in particular against Human Immunodeficiency Virus (HIV), which is the aetiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans. The HIV virus preferentially infects human T-4 cells and destroys them or changes their normal function, particularly the coordination of the immune system. As a result, an infected patient has an everdecreasing number of T-4 cells, which moreover behave abnormally. Hence, the immunological defense system is unable to combat infections and neoplasms and the HIV infected subject usually dies by opportunistic infections such as pneumonia, or by cancers. Other conditions associated with HIV infection include thrombocytopaenia, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as, progressive dysarthria, ataxia and disorientation. HIV infection further has also been associated with peripheral neuropathy, progressive generalized lymphadenopathy (PGL) and AIDS-related complex (ARC).

[0030] The present compounds also show activity against HIV-1 strains that have acquired resistance to art-known non-nucleoside reverse transcriptase inhibitors. They also have little or no binding affinity to human α-1 acid glycoprotein.

[0031] Due to their antiretroviral properties, particularly their anti-HIV properties, especially their anti-HIV-1-activity, the compounds of formula (I) or (I'), their *N*-oxides, pharmaceutically acceptable salts and the stereochemically isomeric forms thereof, are useful in the treatment of individuals infected by HIV and for the prophylaxis of these individuals. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses whose existence is mediated by, or depends upon, the enzyme reverse transcriptase. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic CNS diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis.

[0032] The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, especially HIV-1.

[0033] Apart from their pharmacological properties, the present compounds have interesting physicochemical prop-

erties. For instance, they have a good solubility.

[0034] The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

[0035] It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

[0036] Those of skill in the treatment of HIV-infection could determine the effective daily amount from the test results presented here. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

[0037] The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines and are not intended to limit the scope or use of the invention to any extent.

[0038] Also, the combination of an antiretroviral compound and a compound of formula (I) or (I') can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I) or (I'), and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. Said other antiretroviral compounds may be known antiretroviral compounds such as nucleoside reverse transcriptase inhibitors, e.g. zidovudine (3'-azido-3'-deoxythymidine, AZT), didanosine (dideoxy inosine; ddI), zalcitabine (dideoxycytidine, ddC) or lamivudine (3'-thia-2'-3'-dideoxycytidine, 3TC) and the like; non-nucleoside reverse transciptase inhibitors such as suramine, pentamidine, thymopentin, castanospermine, dextran (dextran sulfate), foscarnet-sodium (trisodium phosphono formate), nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido(3,2-b : 2',3'-e][1,4]diazepin-6-one), tacrine (tetrahydroaminoacridine) and the like; compounds of the TIBO (tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepine-2(1*H*)-one and thione)-type e.g. (S)-8-chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,1-jk][1,4]benzodiazepine-2(1*H*)-thione; compounds of the a-APA (a-anilino phenyl acetamide) type e.g. a-[(2-nitro-phenyl)amino]-2,6-dichlorobenzene-acetamide and the like; TAT-inhibitors, e.g. RO-5-3335 and the like; protease inhibitors e.g. indinavir, ritanovir, saquinovir and the like; or immunomodulating agents, e.g. levamisole and the like.

[0039] The following examples are intended to illustrate the present invention.

Experimental part

A. Preparation of the intermediates

Example A.1

[0040]

a) 2,4,6-trichloro-1,3,5-triazine (0.07440 mol) and tetrahydrofuran (100 ml) were combined and cooled to -75 °C under Ar atmosphere. Then, 4-aminobenzonitrile (0.07440 mol) was added and the solution was stirred for 4 hours. Then,triethylamine (0.07440 mol) was added dropwise and the reaction mixture was allowed to warm up slowly to room temperature and stirred for 3 days. After adding 1,4-dioxane (100 ml), the resulting precipitate was collected by filtration, washed with tetrahydrofuran, and dried, yielding 12.74 g 4-[(4,6-dichloro-1,3,5-triazin-2-yl)amino]benzonitrile (interm. 1).

b) NaH (0.0113 mol), CH_3CN (30 ml) and intermediate (1) (0.0113 mol) were combined and stirred for 15 minutes under Ar atmosphere. Then, 2,6-dichlorophenol (0.0113 mol) was added and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with ice water (30 ml) and filtered. A precipitate formed in the filtrate and was filtered off. The resulting solid was washed with H_2O and CH_3CN, then dried, yielding 0.62 g 4-[[4-chloro-6-(2,6-dichloro-phenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile (interm. 2).

c) *N,N*-diisopropyl-ethylamine (0.00714 mol) was added to a solution of 2-chloro-6-methylbenzenamine (0.00714 mol) in 1,4-dioxane (20 ml) under Ar flow. A solution of intermediate (1) (0.00714 mol) in 1,4-dioxane (5 ml) was added. The reaction mixture was stirred and refluxed for 24 hours. The solvent was evaporated and CH_2Cl_2 was added. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, and the resulting precipitate was filtered off, yielding 0.56 g (21.1%) of 4-[[4-chloro-6-[(2-chloro-6-methylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile (interm. 3).

Example A.2

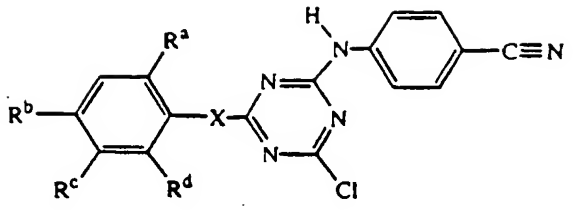
[0041]

a) 2,4,6-trichloro-1,3,5-triazine (0.0266 mol) was added to 1,4-dioxane (50 ml) under Ar atmosphere. The solution was stirred until it became homogeneous, then 2,6-dichlorobenzenamine (0.0266 mol) and K_2CO_3 (0.0362 mol) were added. The reaction mixture was stirred at room temperature for 3 days. The solvent was evaporated. Water was added to the residue and the aqueous phase was extracted with methylene chloride. The separated organic layer was washed with brine, dried with potassium carbonate, filtered and the filtrate was evaporated, yielding 7.52 g (91.2%) of *N*-(2,6-dichlorophenyl)-4,6-dichloro-1,3,5-triazin-2-amine (interm. 4).

b) 1,4-Dioxane (50 ml), 4-cyano-aniline (0.0243 mol), and *N,N*-diisopropyl-ethylamine (0.0243 mol) were added to intermediate (4) (0.0243 mol) under Ar atmosphere. The reaction mixture was stirred and refluxed for 1 week. The solvent was evaporated. Ethyl acetate was added. The organic phase was washed with a saturated $NaHCO_3$ solution and with brine, dried with potassium carbonate, filtered, and the solvent was evaporated. The residue was stirred in a mixture of CH_2Cl_2 and saturated $NaHCO_3$, and filtered off, yielding 2.26 g (23.8%) of 4-[[4-chloro-6-[(2,6-dichlorophenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile (interm. 5).

[0042] Table 1 lists intermediates which were prepared according to one of the above examples.

Table 1



Int. No.	Ex. No.	X	R^a	R^b	R^c	R^d
2	A1b	-O-	Cl	H	H	Cl
3	A1c	-NH-	Cl	H	H	CH_3
5	A2b	-NH-	Cl	H	H	Cl
6	A2b	-NH-	CH_3	H	H	CH_3
7	A1c	-NH-	$CH(CH_3)_2$	H	H	CH_3
8	A1c	-NH-	CH_3	CH_3	H	CH_3
9	A1c	-NH-	C_2H_5	H	H	C_2H_5
10	A1c	-NH-	$C(=O)CH_3$	H	CH_3	H
11	A1c	-NH-	CH_3	Br	H	CH_3
12	A1c	-NH-	CH_3	CH_3	Br	CH_3
13	A1c	-NH-	C_2H_5	H	H	CH_3
14	A1c	-NH-	Br	F	H	F
15	A2b	-NH-	Cl	Cl	H	Cl
16	A1c	-S-	Cl	H	H	Cl

B. Preparation of the compounds of formula (I')

Example B.1

[0043]

a) A mixture of intermediate (8) (0.00137 mol) and NH_3 in 1,4-dioxane (0.5 M; 0.00548 mol) was heated in a pressure vessel at 100 °C for 6 days. The solvent was evaporated and the residue was dissolved in CH_2Cl_2, washed with a saturated aqueous $NaHCO_3$ solution, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0,99/1 and 98/2). The desired fractions were collected and the solvent was evaporated. The residue was recrystallized from toluene. The precipitate was filtered off and dried, yielding 0.29 g (61.4%) of 4-[[4-amino-6-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile (compound 9).

b) As an alternative for the preparation of compound (9), a mixture of intermediate (8) (0.0230 mol) in NH_3 in 2-propanol (2.0 M; 60 ml) and NH_3 in 1,4-dioxane (0.5 M; 20 ml) was heated at 95 °C for 21 hours. The solvent was evaporated. The residue was dissolved in ethyl acetate, washed with 1 N NaOH, water and brine, dried, filtered and the filtrate was evaporated. The residue was recrystallized with acetonitrile, yielding 5.25g (66.1%) of compound (9).

Example B.2

[0044] *O*-(trimethylsilyl)-hydroxylamine (0.0282 mol) was added to intermediate (5) (0.00282 mol) in 1,4-dioxane (10 ml). The reaction mixture was stirred at room temperature for 2 days. The solvent was evaporated. The residue was dissolved in ethyl acetate, washed with 1 N HCl, washed with a saturated aqueous $NaHCO_3$ solution and with brine, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel ((I) eluent: CH_2Cl_2/CH_3OH 96/4 and (II) eluent: CH_2Cl_2/CH_3OH 100/0, 99/1 and 98/2). The desired fractions were collected and the solvent was evaporated. The residue was recrystallized from acetonitrile. The precipitate was filtered off and dried, yielding 0.32 g (29.2%) of 4-[[[6-(2,6-dichlorophenyl)-4-(hydroxyamino)amino]-1,3,5-triazin-2-yl]amino]benzonitrile (compound 4).

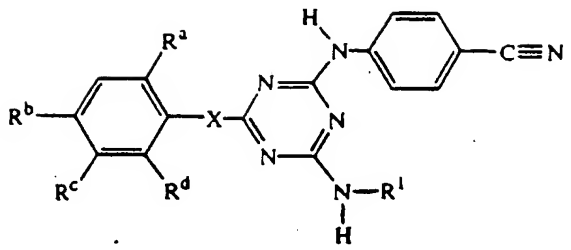
Example B.3

[0045] Tetrahydrofuran (10 ml) and 2,5-dimethyl-phenol (0.00818 mol) were added to NaH (0.00859 mol). The mixture was stirred for 30 minutes at room temperature. Then, a solution of intermediate (1) (0.00818 mol) in tetrahydrofuran (100 ml) was added. The reaction mixture was stirred for 16 hours. Then, the solvent was evaporated and NH_3 in 1,4-dioxane (50 ml) was added. The resulting reaction mixture was stirred for 16 hours. The solvent was evaporated; and, the resulting residue was treated with H_2O/CH_2Cl_2, stirred, and filtered. A precipitate formed in the filtrate and was filtered off, yielding 0.42 g of fraction 1. The resulting filtrate was dried over K_2CO_3 and concentrated. The residue was purified by flash column chromatography (eluent: CH_3OH/CH_2Cl_2 2.5/97.5). The desired fractions were collected and the solvent was evaporated, yielding 2.89 g of fraction 2. Fractions 1 and 2 were combined and recrystallized from CH_3CN.

[0046] The precipitate was filtered off and dried, yielding 1.16 g (42.7%) of 4-[[4-amino-6-(2,5-dimethylphenoxy)-1,3,5-triazin-2-yl]amino]benzonitrile (compound 2).

[0047] Table 2 lists the compounds of formula (I) which were prepared according to one of the above examples.

Table 2



Comp No.	Ex. No.	X	R^1	R^a	R^b	R^c	R^d	melting point
1	B1a	-O-	H	Cl	H	H	Cl	278-279°C
2	B3	-O-	H	CH_3	H	CH_3	H	193-194°C
3	B3	-O-	H	CH_3	H	H	CH_3	235-236°C
4	B2	-NH-	OH	Cl	H	H	Cl	235-236°C
5	B2	-NH-	OH	CH_3	H	H	CH_3	207-210°C
6	B1a	-NH-	H	CH_3	H	H	CH_3	242-244°C
7	B1a	-NH-	H	Cl	H	H	CH_3	130-131°C
8	B1a	-NH-	H	$CH(CH_3)_2$	H	H	CH_3	253-254°C
9	B1a or B1b	-NH-	H	CH_3	CH_3	H	CH_3	151-152°C
10	B1c	-NH-	H	Cl	H	H	Cl	144-145°C
11	B2	-NH-	OH	CH_3	CH_3	H	CH_3	247-248°C
12	B1c	-NH-	H	C_2H_5	H	H	C_2H_5	273-274°C
13	B1c	-NH-	H	$C(=O)CH_3$	H	CH_3	H	255-256°C
14	B1b	-NH-	H	CH_3	Br	H	CH_3	221-222°C
15	B1b	-NH-	H	CH_3	CH_3	Br	CH_3	158-159°C
16	B1b	-NH-	H	C_2H_5	H	H	CH_3	222-223°C
17	B1b	-NH-	H	Br	F	H	F	233-234°C
18	B1b	-NH-	H	Cl	Cl	H	Cl	224-225°C
19	B1b	-S-	H	Cl	H	H	Cl	293-294°C
20	B2	-S-	OH	Cl	H	H	Cl	145-147°C
21	B1a	-NH-NH-	H	Cl	Cl	H	Cl	258-259°C

Comp No.	Ex. No.	X	R^1	R^a	R^b	R^c	R^d	melting point
22	B1a	-NH-NH-	H	Cl	H	H	Cl	246-247°C
23	B2	-NH-	OH	Cl	Cl	H	Cl	262-263°C
24	B1b	-O-	H	CH_3	CH_3	H	CH_3	236-237°C
25	B2	-O-	OH	CH_3	CH_3	H	CH_3	221-222°C
26	B2	-NH-NH-	OH	Cl	Cl	H	Cl	175-176°C
27	B1b	-NH-	H	Cl	CH_3	H	Cl	224-226°C

C. Pharmacological example

Example C.1

[0048] A rapid, sensitive and automated assay procedure was used for the *in vitro* evaluation of anti-HIV agents. An HIV-1 transformed T4-cell line, MT-4, which was previously shown (Koyanagi et al., *Int. J. Cancer*, 36, 445-451, 1985) to be highly susceptible to and permissive for HIV infection, served as the target cell line. Inhibition of the HIV-induced cytopathic effect was used as the end point. The viability of both HIV- and mock-infected cells was assessed spectrophotometrically via the *in situ* reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The 50% cytotoxic concentration (CC_{50} in μM) was defined as the concentration of compound that reduced the absorbance of the mock-infected control sample by 50%. The percent protection achieved by the compound in HIV-infected cells was calculated by the following formula:

$$\frac{(OD_T)_{HIV}-(OD_C)_{HIV}}{(OD_C)_{MOCK}-(OD_C)_{HIV}} \text{ expressed in \%,}$$

whereby $(OD_T)_{HIV}$ is the optical density measured with a given concentration of the test compound in HIV-infected cells; $(OD_C)_{HIV}$ is the optical density measured for the control untreated HIV-infected cells; $(OD_C)_{MOCK}$ is the optical density measured for the control untreated mock-infected cells; all optical density values were determined at 540 nm. The dose achieving 50% protection according to the above formula was defined as the 50% inhibitory concentration (IC_{50} in μM). The ratio of CC_{50} to IC_{50} was defined as the selectivity index (SI). The compounds of formula (I) were shown to inhibit HIV-1 effectively. Particular IC_{50}, CC_{50} and SI values are listed in Table 3 hereinbelow.

Table 3

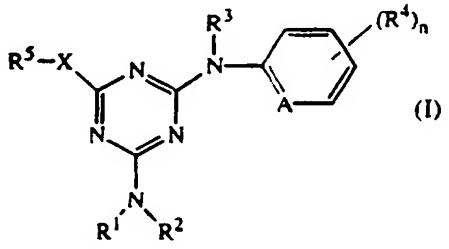
Co. No.	IC_{50} (μM)	CC_{50} (μM)	SI		Co. No.	IC_{50} (μM)	CC_{50} (μM)	SI
1	0.003	>20	>6451		13	0.259	>100	>386
2	0.003	34.9	10750		14	0.003	37.3	11844
3	0.003	33.8	10899		15	0.003	1.7	498
4	0.002	8.0	4187		16	0.006	8.1	1372
5	0.002	7.8	3458		17	0.003	53.8	16311
6	0.004	40.3	11518		18	0.008	45.6	6033
7	0.005	49.9	10187		19	0.004	40.6	11285
8	0.165	9.3	56		20	0.003	11.7	3726

Table 3 (continued)

Co. No.	IC_{50} (μM)	CC_{50} (μM)	SI		Co. No.	IC_{50} (μM)	CC_{50} (μM)	SI
9	0.001	44.0	33826		21	0.001	27.8	27789
10	0.003	6.1	2022		22	0.003	>100	>33333
11	0.001	6.3	4480		23	0.001	7.6	7614
12	0.021	30.0	1449					

Claims

1. The use of a compound of formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

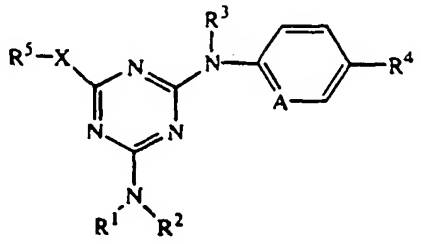
A is CH or N;
n is 0, 1, 2, 3 or 4; and in case A is CH, then n may also be 5;
R^1 and R^2 are each independently selected from hydrogen, hydroxy, C_{1-12}alkyl, C_{1-12}alkyloxy, C_{1-12}alkylcarbonyl, C_{1-12}alkyloxycarbonyl, aryl, amino, mono- or di(C_{1-12}alkyl)amino, mono- or di(C_{1-12}alkyl)aminocarbonyl wherein each of the aforementioned C_{1-12}alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C_{1-6}alkyl)amino, aryl and Het; or
R^1 and R^2 taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C_{1-12}alkyl)aminoC_{1-4}alkylidene;
R^3 is hydrogen, aryl, C_{1-6}alkylcarbonyl, C_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyl substituted with C_{1-6}alkyloxycarbonyl; and
each R^4 independently is hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy;
R^5 is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, cyano, nitro and trifluoromethyl; and
X is $-NR^3-$, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or $-S(=O)_2-$;
aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, cyano, nitro and trifluoromethyl;
Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;

for the manufacture of a medicine for the treatment of subjects suffering from HIV (Human Immunodeficiency Virus) infection.

2. The use of a compound as claimed in claim 1 wherein n is 1 and R^4 is cyano substituted in the 4 position relative to the NR^3 moiety.

3. The use of a compound as claimed in claim 1 or 2 wherein R^5 is phenyl substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl and C_{1-6}alkylcarbonyl.

4. A compound of formula



(I')

a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

the variables R^1, R^2, R^3, R^5, A and X are as defined in claim 1; and
R^4 is cyano, nitro or trifluoromethyl;
with the proviso that

- when R^4 is cyano, R^3 is hydrogen, X is NH, R^5 is 4-cyanophenyl or 4-iodophenyl, then NR^1R^2 is other than NH_2, $NH[CH_2CH_2N(C_2H_5)_2]$, $N(C_2H_5)_2$, $NHCH_3$, NHC_2H_5 or NH(4-cyano-phenyl);
- when R^4 is trifluoromethyl, R^3 is hydrogen, X is NH, R^5 is 4-trifluorophenyl, then NR^1R^2 is other than NH_2 or $N[(CH_2)_6CH_3]_2$;
- when R^4 is nitro, R^3 is hydrogen or methyl, X is NH or N-CH_3, R^5 is 4-fluorophenyl, 2,6-dimethylphenyl, 4-methylphenyl or 4-nitrophenyl, then NR^1R^2 is other than NHaryl, NCH_3aryl, $N(aryl)_2$, NH_2, $NH[CH_2CH_2N(C_2H_5)_2]$, $NH[CH_2CH_2N(CH_3)_2]$, $NH[CH_2C(=O)OC_2H_5]$, $NH[CH_2C(=O)OH]$ or $N(C_2H_5)_2$;
- when R^4 is nitro, R^3 is hydrogen, X is $S(O)_2$ or S, R^5 is phenyl or 4-chlorophenyl, then R^1 and R^2 are other than aryl or C_{1-12}alkyl substituted with one or more carboxyl groups.

5. A compound as claimed in claim 4 wherein R^4 is cyano.

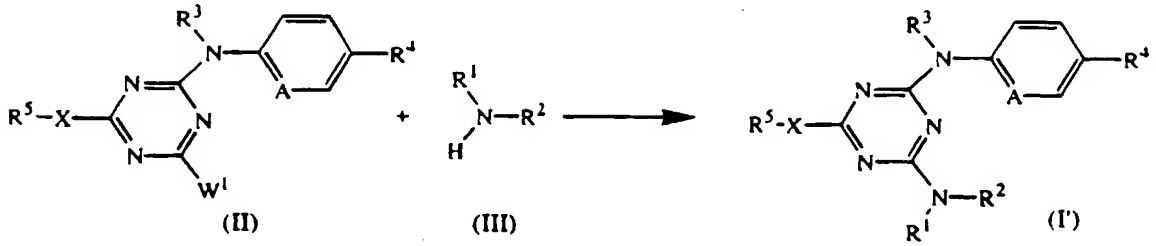
6. A compound as claimed in claim 4 or 5 wherein R^5 is phenyl or phenyl substituted with one, two or three substituents each independently selected from fluoro, chloro, bromo, C_{1-6}alkyl, C_{1-6}alkyloxy, nitro and trifluoromethyl.

7. A compound as claimed in claim 5 or 6 for use as a medicine.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in claim 5 or 6.

9. A process for preparing a pharmaceutical composition as claimed in claim 8 characterized in that a therapeutically effective amount of a compound as claimed in claim 5 or 6 is intimately mixed with a pharmaceutically acceptable carrier.

10. A process for preparing a compound as claimed in claim 4, characterized by reacting an intermediate of formula (II) with an amino derivative of formula (III) in a reaction inert solvent and optionally in the presence of a suitable base;



(II) (III) (I')

wherein W^1 is a suitable leaving group and R^1 to R^5, X and A are as defined in claim 4; or if desired, converting compounds of formula (I') into each other following art-known transformations, and further, if desired, converting the compounds of formula (I'), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms or *N*-oxides thereof.

11. The combination of a compound of formula (I) as defined in claim 1 and another antiretroviral compound.

12. A combination as claimed in claim 11 for use as a medicine.

13. A product containing (a) a compound of formula (I) as defined in claim 1, and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound of formula (I) as defined in claim 1, and (b) another antiretroviral compound.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 20 1589

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	PRAKASH, L. ET AL: "Synthesis of some new trisubstituted derivatives of 2,4,6-trichloro-1,3,5 triazine and their antibacterial activity" PHARMAZIE (1990), 45(4), 284 ;ISSN: 0031-7144, XP002104760 * compound 3h * ---	4,6	C07D251/70 C07D251/52 A61K31/53
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TECHNICAL FIELDS SEARCHED (Int.Cl.6)
C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	3 June 1999	De Jong, B

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EPC FORM 1503 03.82 (P04C01)

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X	CHEMICAL ABSTRACTS, vol. 108, no. 15, 11 April 1988 Columbus, Ohio, US; abstract no. 131766, KREUTZBERGER, ALFRED ET AL: "Anticonvulsives. IV. 2,4,6- mixed functional substituted 1,3,5-triazine" XP002104762 * abstract * -& DATABASE CHEMABS CA108:131766, XP002104767 * RN=113401-46-0 * & CHEM.-ZTG. (1987), 111(7-8), 241-5 CODEN: CMKZAT;ISSN: 0009-2894, ---	4,6	
X	CHEMICAL ABSTRACTS, vol. 98, no. 11, 14 March 1983 Columbus, Ohio, US; abstract no. 89321, LANGALIA, N. A. ET AL: "Studies on antitubercular agents. Part III. Preparation of some p-(2,4-diarylamino-6-S-triazinylamino)-benzaldehyde/acetophenone thiosemicarbazones as potential tuberculostatic agents" XP002104763 * abstract * -& DATABASE CHEMABS CA98:89321, XP002104768 * RN=84688-78-8 * & J. INDIAN CHEM. SOC. (1982), 59(9), 1099-101 CODEN: JICSAH;ISSN: 0019-4522, --- -/--	4,6	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

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X	CHEMICAL ABSTRACTS, vol. 95, no. 4, 27 July 1981 Columbus, Ohio, US; abstract no. 25685, UNISHI, TERUNOBU ET AL: "Preparation of polypyromellitimides containing dialkylamino-type melamine units" XP002104764 -& DATABASE CHEMABS CA95:25685, XP002104769 * RN=78123-93-0 * & NIPPON KAGAKU KAISHI (1981), (4), 565-8 CODEN: NKAKB8;ISSN: 0369-4577, ---	4,6	
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X	FR 2 099 730 A (GEIGY AG J R) 17 March 1972 * page 5; claim 8 * ---	4,6	
A	EP 0 795 549 A (AMERICAN CYANAMID CO) 17 September 1997 * claims * --- -/--	1	

The present search report has been drawn up for all claims

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THE HAGUE	3 June 1999	De Jong, B

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A	ASHLEY J N ET AL: "THE SEARCH FOR CHEMOTHERAPEUTIC AMIDINES. PART XVI AMIDINOANILINO-1,3,5-TRIAZINES AND RELATED COMPOUNDS" JOURNAL OF THE CHEMICAL SOCIETY, 1 January 1960, pages 4525-4532, XP000573907 * compounds of formula V *	4	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
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P : intermediate document

T : theory or principle underlying the invention
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